Remarks

Entry of this amendment is respectfully requested. Claims 56-68, 78-86, 118 and 119 are pending in the instant application. Claims 56-68, 78-86, 118 and 119 stand rejected. Claims 57 and 68 are cancelled without prejudice or disclaimer to the subject matter contained therein. Claim 56 is amended herein. Support for the amendments can be found, for example, at page 3, lines 22 to 27. Applicants respectfully request reconsideration and withdrawal of the rejections for the reasons set forth herein. There is no issue of new matter.

The amended claims are directed to a method for screening a first repertoire of antibody heavy chain or antibody light chain polypeptides against a second repertoire of antibody heavy chain or antibody light chain polypeptides to identify those members of the first repertoire which interact with members of the second repertoire, comprising the steps of:

a. arranging the first repertoire in at least one first series of continuous lines wherein each line of said first series comprises a member of said first repertoire;

b. arranging the second repertoire in at least one second series of continuous lines wherein each line of said second series comprises a member of said second repertoire;

c. forming an array of a plurality of first and second repertoires from step a and step b, wherein said first series of continuous lines from step a intersects with a plurality of said second series of continuous lines from step b, and wherein all members of the first repertoire are juxtaposed to all members of the second repertoire; and

d. detecting an interaction between the antibody heavy chain or antibody light chain of the first and second repertoires, thereby identifying those members of the first repertoire that interact with members of the second repertoire.

In view of the foregoing remarks and the claims as amended, the Applicant's respectfully request that the Examiner withdraw her rejections based on 35 USC §103 because the current amended claims render these rejections moot.

Claim Rejections Under 35 USC § 103

The Office action states that Claims 56-68, 78-86, and 118-119, are rejected under 35 U.S.C. 103(a) as being unpatentable over Feldstein et al. (U.S. Patent 6,192,168 filed April 9, 1999); Dower et al. (U.S. Patent 5,427,908 issued June 27, 1995); and McCafferty et al. (U.S. Patent 5,969,108 issued October 19, 1999).

Specifically, the Examiner suggests that Feldstein et al. teach a microfluidic device for multianalyte interactions wherein a multimode waveguide (i.e., solid surface) is paired with a fluidic cell to perform multianalyte and multisample assays. Furthermore, the Examiner suggests that Dower et al. teaches methods of screening single-chain polypeptides for binding comprising producing a library of antibody light chains and a library of antibody heavy chains, combining the heavy and light chains and screening for antigen binding wherein the antibody heavy and light chains are produced via phage display utilizing bacteria cells for propagation and the heavy and light chains can be expressed by the same phage or different phage. The Examiner concedes, however, that "Feldstein et al. does not teach a first repertoire of antibody heavy chains and a second repertoire of antibody light chains." In addition, the Examiner concedes that Feldstein et al. nor Dower et al. teach single chain polypeptides comprising both VH and VL or dAb. However, the Examiner goes on to allege that McCafferty et al. overcome these deficiencies. Briefly, the Examiner characterizes McCafferty et al. as teaching methods of screening libraries of scFv and dAb for binding utilizing phage display.

The Examiner concludes that it would have been *prima facie* obvious to one skilled in the art to "because the substitution of one known element (i.e. antibody; multimer, Feldstein et al.) for another (i.e. separate VH and VL, scFv, or dAb taught by Dower et al. and/or McCafferty et al.; utilization of scFv in sandwich assay taught by Feldstein et al.) would have yielded predictable results (i.e. VH-VL binding, antibody-antigen binding, etc.) to one of ordinary skill in the art at the time of the invention.

Without conceding the validity of this rejection, Applicants have elected to present the invention in different terms, which terms obviate the asserted basis for this rejection. Applicants respectfully assert that due to the amendments made to the

existing claims, this rejection is now moot. Applicants have cancelled Claims 57 and 68.

In a proceeding before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. See *In re Piasecki*, 745 F.2d 1468, 1471-73, 223 U.S.P.Q. 785 (Fed. Cir. 1984). To establish a *prima facie* case of obviousness, the Examiner must show that the cited references teach or suggest all the features recited in the claim. As set forth in *Graham v. John Deere Co. of Kansas City*, "under § 103, the scope and content of the prior art to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17, 148 U.S.P.Q. 459 (1966). Even if the combination of references teaches each feature of the claimed invention, the Examiner must provide some articulated reasoning with some rational underpinning regarding why a person having ordinary skill in the art would have combined the cited references to obtain the subject matter claimed by the Applicant as of the time that the Applicants made the claimed invention. *See KSR v. Teleflex, Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (Fed. Cir. 2007). The Examiner must also show that, in view of the cited art at the time of Applicants' invention, a person having ordinary skill in the art would have had a reasonable expectation of successfully arriving at the claimed subject matter. *See id.* at 1740; *see also* Manual of Patent Examination Procedure (M.P.E.P.) § 2143.02 (*citing In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986)).

The Applicants respectfully submit that none of the cited references teach each of the features of the currently amended claims. Moreover, they do not provide a rational underpinning for creating a method for screening a first repertoire of antibody heavy chain or antibody light chain polypeptides against a second repertoire of antibody heavy chain or antibody light chain polypeptides to identify those members of the first repertoire which interact with members of the second repertoire, comprising the steps of:

a. arranging the first repertoire in at least one first series of continuous lines wherein each line of said first series comprises a member of said first repertoire;

b. arranging the second repertoire in at least one second series of continuous lines wherein each line of said second series comprises a member of said second repertoire;

c. forming an array of a plurality of first and second repertoires from step a and step b, wherein said first series of continuous lines from step a intersects with a plurality of said second series of continuous lines from step b, and wherein all members of the first repertoire are juxtaposed to all members of the second repertoire; and

d. detecting an interaction between the antibody heavy chain or antibody light chain of the first and second repertoires, thereby identifying those members of the first repertoire that interact with members of the second repertoire. The Applicants wish to direct the Examiner to, for example, page 1-9 of the present specification for an introduction to the benefits of the present invention over the prior art.

The combination of Feldstein et al., Dower et al., and McCafferty et al. fails to describe each element of the claimed invention. Applicants assert that Feldstein et al. describes optical waveguide devices for detection of samples and analytes (e.g. abstract and claims) and goes on to detail multimode waveguides paired with a fluidics cell which allows optical measurements to be performed on the surface of the waveguide. The fluidics cell contains at least one channel for the flow of a fluid sample over the optically exposed region of the waveguide.

The present claims specify methods for screening a first repertoire of antibody heavy chain or antibody light chain polypeptides against a second repertoire of antibody heavy chain or antibody light chain polypeptides to identify those members of the first repertoire which interact with members of the second repertoire. There is no teaching or suggestion in Feldstein et al. of any repertoires of molecules, and certainly not repertoires of antibody heavy and light chains and no mention of the arrangement of the repertoires as specified in the present claims.

Applicants assert that Dower et al. is in a different field to the above, which teaches using libraries of heavy and light chains of antibodies to identify binding pairs.

The Examiner has not presented evidence that one having ordinary skill in the art would have been motivated to combine the teachings Dower et al. and Feldstein et al. in the proposed manner to arrive at the claimed invention. That is, there is no motivation in Dower et al. for the skilled artisan to discount the methods of Dower et al. and to adapt the teachings of Feldstein et al. to screen two repertoires to identify molecules which interact. Dower et al. provides different methods for looking at interactions between molecules to that of the present invention. For example, it describes using bacteriophage expression vectors to express Fabs and to then screen these against ligands of interest (see claim 1 of Dower). This is clearly different to the methods of the present claims which arrange the repertoires in continuous lines such that a first series comprising the first repertoire and a second series of continuous lines comprises the second repertoire and they intersect as required by the claims. Furthermore, Dower is not teaching simultaneous screening of two repertoires against each other. Rather Dower describes a simple screening method of Fabs to determine whether they react with a ligand of interest.

Similarly McCafferty et al. discloses phage display methods which are entirely different from the claimed screening methods for identifying members of specific binding pairs. There is no motivation for the skilled artisan to discount the methods of Dower and to adapt the teachings of Feldstein to screen two repertoires to identify molecules which interact. McCafferty et al. uses phage display methods for screening to identify members of specific binding pairs. Nowhere does McCafferty et al. teach or suggest screening of two repertoires against each other. This is clearly entirely different to the methods of the present claims which do screen two repertoires against each other and arrange the repertoires in continuous lines such that a first series comprises the first repertoire and a second series of continuous lines comprises the second repertoire and they intersect as required by the claims.

Thus, the claimed invention would not even have been “obvious to try” under the *KSR* standard. Accordingly, the combination of Feldstein et al., Dower et al., and McCafferty et al. references fails to teach or suggest the claimed method.

Because the combination of Feldstein et al., Dower et al., and McCafferty et al. does not arrive at the claimed invention, a *prima facie* case of obviousness over the amended claims can not be established. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §103.

The Office action states that Claims 56-68, 78-86, and 118-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowe et al. Anal. Chem. 71(2): 433-439, 1999; Stevens et al. U.S. Patent 6,485,943 filed March 22, 1999; and McCafferty et al. U.S. Patent 5,969,108 issued October 19, 1999.

The Examiner suggests that for "claims 56-57, 62-68, and 86, Rowe et al. teach methods of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor wherein vertical channels comprise antibodies and adding samples flowed through horizontal channels (first repertoire) wherein the vertical and horizontal channels (first repertoire and/or second repertoire) wherein the vertical and horizontal channels are at 90° angles (please refer to entire reference particularly Figure 1; experimental section)." The Examiner concedes that "Rowe et al. does not specifically teach utilizing VH or VL in separate channels (i.e. multimer antibodes are utilized)."

In addition, the Examiner suggests that for "claims 59-61, Stevens et al. teach methods of making recombinant antibody subunit dimmers including VH-VL and VL-VL and screening against antigen comprising providing VH and/or VL and interacting the VH and/or VL (referring to entire specification particularly abstract; column 4, lines 44-67; column 5, lines 1-9; lines 1-9; column 6, lines 20-41; column 7, lines 23-36; columns 9-10)."

The Examiner further concedes that "neither Rowe et al. nor Stevens et al. teach dAb (i.e. specifically, VH and VL are taught by Stevens et al.) or phage display."

In addition, the Examiner suggests that for "claims 58-61, 78-86, and 118-119, McCafferty et al. teach methods of screening libraries of scFv and dAb for binding utilizing phage and propagation in bacterial cells (referring to the entire specification particularly Figure 1; column 11;Examples 1-48)."

The Examiner further suggests that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor taught by Rowe et al. with the VH-VH or VL-VL taught by Stevens et al. and the dAb and phage display taught by McCafferty et al."

The Examiner further suggests that "[o]ne having ordinary skill in the art would have been motivated to do this because Rowe et al. teach that immunosensors are easy to use, provide rapid assay times, have sensitivity comparable to ELISA, and can be utilized to study multianalyte binding (referring to introduction and conclusion sections). In addition, Stevens et al. teach homologous dimerization of antibody subunits and altering amino acid sequences in the interfacial segments to improve yields of Fab and Fv products and studying the interactions via dimerization assay/screens (referring to columns 4-5)."

The Examiner further suggests that '[o]ne of ordinary skill in the art would have had a reasonable expectation of success in the modification of the method of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor taught by Rowe et al. with the VH-VH or VL-VL taught by Stevens et al. and the dAb and the phage display taught by McCafferty et al. because Rowe et al. teach utilizing immunosensors to study multianalyte interaction (e.g. VH, VL antigen, dimmers, trimers, referring to the conclusion)."

In addition, the Examiner suggests that "the claims would have been obvious because the substitution of one known element (i.e. antibodies taught by Rowe et al. and Stevens et al.) for another (i.e. antibodies displayed via phage as taught by McCafferty et al.) would have yielded predictable result (i.e. VH-VL binding, antibody-antigen binding, etc.) to one of ordinary skill in the art at the time of the invention. See *KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007)."

Finally, the Examiner states that "the modification of the method of producing two-chain or three-chain polypeptides comprising utilizing an array immunosensor taught by Rowe et al. with the VH-VH or VL-VL taught by Stevens et al. and the dAb

and phage display taught by McCafferty et al. render the instant claims *prima facie* obvious."

In view of the Supreme Court's recent decision in *KSR Int'l v. Teleflex Inc.*, where the Examiner alleges that the claimed invention is a combination of prior art elements according to known methods, the Examiner must articulate the following:

> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference:
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
> Federal Register Vol. 72, No. 195: 57256, at 57529.

"If any of these findings cannot be made, then this rationale *cannot* be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." *Id.* (emphasis added)

The hallmark of obviousness is predictability. A combination of prior art elements is obvious only if the combination does no more than yield predictable results. Conversely, it stands to reason that if the results of the combination are unpredictable (either inherently or technically), the combination is not obvious. Thus, the question to be asked in evaluating obviousness of the instant claims is not simply whether the

individual elements of the claims can be found in the prior art, but whether their combination would have been predicted to yield the desired results.

In the present case, the answer to that question is no. Applicants assert that Rowe et al. teach an immunoassay performed using an immunosensor. In this immunoassay three specific chosen antibodies for detection are labelled with biotin for immobilisation to the sensor surface. These are then used to screen samples for the presence of three different analytes. This immunoassay method is different from the present invention's repertoire based screening method. Rowe et al. relates to screening of a final product/analyte by a specific antibody. It does not describe or suggest use of any repertoires of molecules and of screening these against each other, nor does it mention or suggest arranging the first repertoire in at least one first series of continuous lines wherein each line of said first series comprises a member of said first repertoire; arranging the second repertoire in at least one second series of continuous lines wherein each line of said second series comprises a member of said second repertoire; forming an array of a plurality of first and second repertoires from step a and step b, wherein said first series of continuous lines from step a intersects with a plurality of said second series of continuous lines from step b, and wherein all members of the first repertoire are juxtaposed to all members of the second repertoire; and detecting an interaction between the antibody heavy chain or antibody light chain of the first and second repertoires, thereby identifying those members of the first repertoire that interact with members of the second repertoire as described in the current application.

By contrast, Stevens et al. teach methods of making recombinant antibody dimers in which at least one codon of a nucleic acid sequence is modified (abstract) and hence is different from Rowe et al. (which describes an immunoassay using an immunosensor for detection purposes). Like Rowe et al., Stevens et al. also does not teach or suggest making any polypeptide repertoires. Were the skilled artisan to read Stevens et al. they would have likely used the methods described therein to produce antibody dimmers. For example, they would have made the specified mutations in the particular positions as described in Stevens et al. The skilled person would not have read Rowe et al., Stevens et al., and McCafferty et al. (as described above) and have

been motivated to abandon these teachings and instead make repertoires of molecules as described by the present application and then screen these against one another.

In view of the foregoing remarks and claim amendments, the Applicant respectfully requests that the Examiner withdraw her rejection based on 35 U.S.C. §103.

Double Patenting

Claims 56-68, 78-86, and 118-119 are provisionally rejected on the ground of nonstatury obviousness-type double patenting as being unpatenable over claims 1 and 3-23 of copending Application No. 11/413,427.

Applicants respectfully assert that this rejection is now moot. Specifically, the status of Applicantin No. 11/413,427, was updated on PAIR as abandoned on August 19, 2009.

Claims 56-68, 78-86 and 118-119 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, and 14-44 of copending Application No. 10/161,145. In the Examiner's opinion, although the conflicting claims are not identical, they are not patentably distinct from each other. The Examiner states that the present invention and the invention of Application No. 10/161,145 are drawn to methods comprising arraying a plurality of polypeptides on a support which can be single-chain or two-chain, arraying a second plurality of peptides/targets on a support which can be single-chain, and juxtaposing the supports so that either two-chain or three-chain polypeptides are produced.

Applicants maintain that they will address this rejection if claims in U.S. Patent Application No. 10/161,145 that are deemed to be conflicting are allowed prior to the patenting of the claims in this application. If this provisional rejection is the only rejection remaining after entry and consideration of this Amendment, Applicants request that the Examiner permit the subject application to issue as a patent, in accordance with U.S. Patent Office procedure (see, MPEP § 804(I)(B)).

The Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending and new claims is earnestly solicited. If it would expedite prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned attorney.

Respectfully submitted,

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